Inverse mismatch and lesion growth in small subcortical ischaemic stroke

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Abstract: OBJECTIVE: Infarction typically develops within the borders of an initial hypoperfused tissue. We prospectively investigated whether in small subcortical stroke patients infarct growth can occur beyond the margins of the affected vascular territories. METHODS: In 19 consecutive patients, stroke MRI was performed within 14 h after ictus, and at days 2 and 6 (± 1). Size of diffusion and perfusion disturbances were determined. Infarct volume measured on T2-weighted images on day 6 was considered as imaging endpoint. RESULTS: At the initial examination, the mean diffusion lesion [apparent diffusion coefficient (ADC) lesion size, 1.82 ± 1.2 ml] was larger (p = 0.0002) than the perfusion lesion [mean transit time (MTT) lesion size, 0.72 ± 0.69 ml]. Such an "inverse mismatch" (ADC lesion > MTT lesion) was present in 14/19 patients at baseline and in all patients on day 2. Final lesion volume at day 6 was 3.2 ± 1.6 ml which was larger than the initial perfusion deficit (p = 0.02). CONCLUSION: In small subcortical ischaemic stroke "inverse mismatch" is frequent and infarction develops beyond the initial perfusion disturbance. This indicates that cytotoxic processes probably triggered by the infarct core are a dominant mechanism for lesion growth. Areas with normal perfusion but which are threatened by cytotoxic damage developing over several days seem prime targets for neuroprotective therapy.

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Abstract

Objective: Infarction typically develops within the borders of an initial hypoperfused tissue. We prospectively investigated whether in small subcortical stroke patients infarct growth can occur beyond the margins of the affected vascular territories.

Methods: In 19 consecutive patients, stroke MRI was performed within 14 hours after ictus, and at days 2 and 6 (±1). Size of diffusion and perfusion disturbances were determined. Infarct volume measured on T2-weighted images on day 6 was considered as imaging endpoint.

Results: At the initial examination, the mean diffusion lesion (ADC lesion size: 1.82±1.2 ml) was larger (p=0.0002) than the perfusion lesion (MTT lesion size: 0.72±0.69ml). Such an "Inverse Mismatch" (ADC lesion > MTT lesion) was present in 14/19 patients at baseline and in all patients on day 2. Final lesion volume at day 6 was 3.2±1.6ml which was larger than the initial perfusion deficit (p=0.02).

Conclusion: In small subcortical ischaemic stroke "Inverse Mismatch" is frequent and infarction develops beyond the initial perfusion disturbance, This indicates that cytotoxic processes probably triggered by the infarct core are a dominant mechanism for lesion growth. Areas with normal perfusion but which are threatened by cytotoxic damage developing over several days seem prime targets for neuroprotective therapy.

Introduction

A reason for the failure of many clinical trials in acute stroke is the pronounced heterogeneity of underlying pathophysiological processes. These differ not only *between* patients, but also continuously change in an individual patient over time. Thus, therapeutic approaches which are beneficial in one pathophysiological condition may be harmful in another situation either in another patient or in the same patient at a different time point. A well known example is the presence/absence of a penumbra region, i.e. an area in which perfusion is reduced and functional and metabolic disturbances have occurred, but which is not yet irreversibly damaged. Aggressive reperfusion therapy, most notably fibrinolysis, can only be useful if there is threatened tissue to be saved.

Following these considerations, imaging methods have been developed to identify the ischaemic penumbra and to tailor (fibrinolytic) therapy accordingly. In stroke MRI an operational definition of the penumbra is derived from perfusion and diffusion imaging: In the acute phase of ischaemic stroke, increased signal on diffusion-weighted imaging (DWI) with an initially normal appearance on T2 images indicates areas in which anoxic depolarisation of brain cells has occurred due to severe metabolic damage, i.e. the "core zone" [1-4]. The surrounding hypoperfused but still viable cerebral tissue is characterised by a prolonged capillary mean transit time (MTT) in dynamic susceptibility perfusion MRI (PI). The difference between lesion sizes on MTT maps and DWI ("***mismatch***") is considered a surrogate marker of the ischaemic penumbra ("tissue at risk"), i.e. an area known to potentially benefit from early reperfusion [5-9].

For territorial infarcts, this pathophysiological pattern of "core and penumbra/mismatch" has now been confirmed by several clinical studies. The underlying reason for this pathophysiological pattern is the presence of significant collateral circulation which limits a

sharp reduction of perfusion to only a portion of the affected vascular territory ("core zone"), while in surrounding regions perfusion is maintained by collateral circulation.

Such collateral vascular supply may not be present in small subcortical infarcts (SSI) which involve the small terminal vessels of the subcortical cerebrum and brainstem [10]. They are typically characterised by a regular shape that is frequently rounded or tube-like with a diameter of 0.2 - 2 cm [11-13]. SSI account for up to 25% of all strokes [14] and occur predominantly in patients with small vessel disease, such as diabetes and hypertension [10]. Steinke evaluated the impact of different types of infarction on the clinical time course of patients [15]. Out of a group of 92 stroke patients with severe motor deficits, 24% had significant worsening of motor function. This worsening was associated with lacunar stroke which was present in 59% of patients suffering from worsening.

There have been only a few MRI studies of small subcortical infarcts [14, 16-24]. Only Gerraty et al. (2002) and Doege et al. (2003) investigated the mismatch area of SSI. In the series of Gerraty et al. 10 out of 17 patients with SSI had a perfusion deficit which was smaller than the DWI lesion [21]. In two cases, they observed that infarction spread beyond its initial extent without any perfusion deficit. Doege et al. reported an "***inverse mismatch***" (DWI>PI) in six patients and a further increase in DWI lesion size as well as perfusion deficit within the following 24 hours [24]. Final infarct size after one week was larger than the area of hypoperfusion in the acute phase and at the follow-up examination.

Motivated by those previous preliminary observations, we attempted to systematically evaluate two key features of a potentially different pathophysiology in SSI: (1) The presence of an "Inverse Mismatch" and (2) lesion growth beyond the area of an initial deficit during the first week after stroke onset. We hypothesise that such fundamentally different pathophysiological patterns might need different therapeutic approaches like neuroprotective substances.

Materials and methods

Patients

Nineteen consecutive patients (mean age 65 years, range 42-78) with symptoms indicative of acute SSI were enrolled into this prospective study according to a prospective screening protocol. Patients presenting with clinical signs of acute stroke and a NIHSS score higher than 2 were examined with CT. In the case of a negative CT for both haemorrhagic and ischaemic stroke patients were imaged with MRI according to our institutional protocol [24]. Patients with any contraindication to MRI were excluded. None of the patients received thrombolytics or participated in any randomised clinical trial. All patients were treated on a certified stroke unit according to European guidelines. The patients underwent MRI imaging acutely (< 14:05 hours, mean 6:08 h), after 24 hours and 6 ± 1 days after the onset of symptoms. Perfusion imaging was done on days 1 and 2. Written informed consent was obtained from the patient or a relative of the patient. The study design was approved by the ethics committee of the Charité Hospital, Berlin.

MR Imaging Protocol

Magnetic resonance imaging was performed on a 1.5 T scanner (Vision®, Siemens Medical Systems, Erlangen, Germany). Examinations included DWI, PI (first and second examination), and T1- and T2 weighted imaging. The total imaging time was about 20 min.

For DWI, we used a spin-echo diffusion-weighted echo-planar imaging sequence (TR/TE 4657/118 ms; matrix 128 x 128; 20 slices; field of view 240 mm; slice thickness 6 mm; gap 0.6 mm; diffusion gradients in three orthogonal directions) with two different b values (0 s/mm^2 and 1000 s/mm^2). For T2-weighted imaging, a multi-echo turbo spin-echo sequence (TR/TE, 2900/(15, 75, 135) ms; matrix 256 x 256; 20 slices; FOV 240 mm; slice thickness 6

mm; gap 0.6 mm) was employed. Perfusion imaging was performed by using T2*-weighted echo-planar sequences (TR/TE = 1000/54 ms; matrix 128 x 128; 6 slices; FOV 240 mm; slice thickness 6 mm; gap 0.6 mm). The six transverse sections always covered the infarcted area and were positioned in the same plane as for DWI. A bolus of 20 ml of Magnevist® (gadopentetate dimeglumine; Schering, Berlin, Germany) i.e. a dose of 0.1 mmol/kg/bw followed by 20 ml saline were injected into an antecubital vein at 4 ml/s with a power injector (Spectris; MEDRAD, Warrendale, PA, USA). MR data acquisition started at the beginning of the contrast agent injection at a temporal resolution of 1 batch/s and was continued for 60 seconds. All image slices were positioned in anterior-posterior commissure orientation.

Postprocessing of the Imaging Data

The voxelwise calculation of the mean transit time (MTT) was performed by using the normalised first moment of the logarithmic signal intensity time course [25, 26]. The isotropic DWI was calculated voxelwise as the mean DWI of three orthogonal directions.

Manual Marking of the Ischaemic Areas

One experienced observer highlighted the infarct area using the software program Analyze® 5.0 (Mayo Clinic, USA). The observer (JBF) had no clinical information. In a semi-automated fashion the observer had to point in the centre of the lesion and choose qualitatively the pixel intensity value considered to be the border between “normal” and “infarct”. All infarctions diagnosed at day one presented with ADC values below 650 10^{-6} x mm^2/s.

The ROI itself was then described as the equivalence line of this border intensity. If this line included areas that do not belong to the SSI from the observer’s point of view voxels were excluded. Isotropic diffusion-weighted and T2-weighted images from three examinations and MTT maps from the first two examinations were evaluated from every patient. All initial sizes of infarct areas were normalised to the final lesion volume (FLV), defined by T2-weighted

images from day 6. After determining the volumes we tested differences between initial MTT and DWI lesion for significance using a Wilcoxon test.

Results

The initial diffusion lesion had a mean volume of 1.82 ml (SD 1.2ml) and mean perfusion deficit on MTT maps was 0.72 ml (SD 0.69ml). The difference between DWI and MTT lesions was highly significant (p=0.002) and indicates an inverse mismatch between hypoperfusion and infarction. On day 2, mean diffusion lesion volume increased to 2.78 ml (SD 1.39ml) causing an inverse mismatch in each of the 19 patients ($p < 0.0001$). Final lesion volume (FLV) at day 6 ranged from 0.64 ml to 6.0 ml (mean 3.2ml; SD 1.6ml). It was a median 1.69 times larger than the initial DWI lesion and 3.63 times larger than the initial perfusion deficit (mean values: 2.33 and 5.23 respectively).

Compared with final infarct volume, the initial diffusion lesion was 55.7 FLV% (SD 34.3%) and the mean initial MTT deficit was 24.7 FLV% (SD 21.6%). Contrary to lesion growth on DWI, the MTT deficit showed no change (p=0.98) from day 1 (24.7 FLV%) to day 2 (23.6 FLV%).

Patients were divided into three groups based on initial imaging findings: 'match' (0M), 'mismatch' (MM), 'inverse mismatch' (IM). The group 0M contained three patients (median NIHSS 3; range 3-6) in whom initial DWI lesion and MTT deficit volumes differed less than 20%. Two patients were classified as MM (median NIHSS 6.5; values 2, 11), with the initial MTT deficit exceeding initial DWI lesion more than 20%. IM with initial DWI at least 20% larger than initial MTT was observed in 14/19 patients and are illustrated in figure 1 (median NIHSS 4.5; range 2-11). All lesion volumes are shown in table 1.

In all 0M and MM cases the size of the diffusion lesion increased significantly from 20.1 FLV% at day 1 to 99.4 FLV% at day 2 ($p < 0.043$). MTT deficit was smaller than FLV at day

1 (40.2 FLV%) and decreased further at day 2 (12.2 FLV%) in 0M and MM patients. In the 0M group, initial DWI lesion and MTT deficit were each 25% of FLV. In the MM group, the initial DWI lesion was 12.6 FLV% and the initial MTT was 61.94 FLV%.

The diffusion lesion volume in the IM group increased from 68.4 FLV% at day 1 to 91.2 FLV% at day 2 (significance at p=0.001). MTT deficit slightly increased from 19.2 FLV% at day 1 to 27.8 FLV% at day 2 (p=0.981).

Discussion

We propose that in patients with subcortical ischaemic stroke (SSI), pathophysiology in the affected cerebral regions differs fundamentally from the well known pattern in territorial infarcts. Specifically, we show here that "inverse mismatch" occurs very frequently in SSI and that infarction spreads into areas outside the initial ischaemic territory. We hypothesise that these imaging findings not only reflect different pathophysiological processes but most likely also imply different therapeutic strategies.

Before discussing the pathophysiological implications of our findings, we consider potential methodological reasons. Specifically, one may ask whether our MTT measurement has underestimated the true size of the initial perfusion disturbance. The postprocessing of perfusion images was conducted according to the widely used algorithm by Ostergaard et al [25, 26], where a block circulant correction was not conducted [27]. However, using a block circulant correction would lead to even smaller perfusion deficits. Yamada et al. presented a detailed comparison of different postprocessing algorithms in stroke patients suffering from large vessel disease [28]. In acute stroke, MTT based on singular value decomposition (SVD) led to a sensitivity of 94% and a negative predictive value of 97% for future infarction. Therefore, an underestimation of the real extent of ischaemia based on MTT maps is unlikely. Inverse mismatch is based on the finding that a perfusion deficit is smaller than a given DWI

lesion. The qualitative MTT map we used carries the risk of overestimation – thus decreases the chance of identifying inverse mismatch. Furthermore, in our earlier preliminary study by Doege et al. in a group of 6 patients with SSI [24] in which we had observed an inverse mismatch, we were able to show that even if the threshold for a perfusion disturbance was set at only -25% decrease in blood flow the perfusion lesion was smaller than the diffusion lesion.

The manual delineation of diffusion lesions and perfusion deficits is another potential source of error in our study. To obtain reliable results all readings were performed under identical conditions with the same hardware and window settings and by an observer blinded to the clinical patient data. Luby et al. demonstrated an excellent reading accuracy if experienced readers evaluate stroke images in a standardised setting [29]. Another limitation of our approach might be the slice thickness of 6 mm. However, the typical shape of a lacunar infarction is perpendicular to the imaging slices and thus the in-plane resolution has more influence on the determination of the volume. Future studies at 3T would allow higher spatial resolution and would overcome this limitation.

When evaluating the "validity" of non-invasive imaging findings in acute stroke, the issue of practical "usefulness" for clinical decision making is frequently confused with the precise pathophysiological correlates of the surrogate parameters which are derived from MR measurements. For example, for the *practical* purpose of clinical decision-making in acute ischaemic stroke, the presence of a mismatch area is regarded as an argument in favour of performing aggressive reperfusion therapy (i.e. fibrinolysis). For this intended practical purpose, studies like the DEFUSE study [9] support the validity of the mismatch concept in large vessel disease. Based on the imaging findings from 74 patients the likelihood of benefit from reperfusion was predicted by the presence/absence of mismatch at 3-6 hours of stroke.

Usefulness in clinical decision making, however, does not necessarily imply that all the pathophysiological assumptions are also valid and indeed, the precise relationship between

the surrogate markers “diffusion-lesion” and “mismatch” and the underlying pathophysiological events is by far not as clear cut. Thus, the “Core Zone” as derived from DWI does not always indicate irreversible damage; on the other hand, reversible diffusion lesions have been reported, particularly during the first three hours after onset of ischaemia [30]. Furthermore, the “mismatch” region is not congruent with the ischaemic penumbra, e.g. the former may include regions with only minor reduction of blood flow and thus no significant disturbance of metabolism. Comparisons with PET findings have illustrated the difference between the two [31, 32].

Despite these imprecision some important statements about lesion evolution can be made with high validity and predictive value based on DWI/PI findings in territorial infarction: (i) The typical mismatch finding in the acute phase of ischaemic stroke is followed by a period in which the core zone grows, however, only within the area of the initial perfusion disturbance and thus, (ii) the size of the final infarct does not exceed the size of the initial perfusion lesion. (iii) Only in the case of rapid reperfusion may a diffusion lesion be larger than the perfusion deficit. Thus, our findings in a group of 19 consecutive patients with small subcortical ischaemic stroke are completely different. An inverse mismatch was already found at the initial examination in three quarters of the patients and about 24 hours later, all patients showed this constellation.

If pathophysiological concepts of territorial ischaemia are applied to explain this finding, one would have to assume spontaneous reperfusion in each of these subjects, i.e. in three quarters of the patients already at the first examination, in the remaining patients between the first and second examinations. While such a consistent pattern of reperfusion would be different from all we know in territorial infarction this would also not explain why infarct growth occurred beyond the area of initial perfusion deficit *and* diffusion lesion. Thus, early reperfusion seems not only unlikely to have occurred in all subjects so early, but even if it did, this would not explain the observed lesion evolution. Pairwise comparison between subcortical ischaemic

stroke to small cortical ischaemic stroke would have been a model to study the two different concepts of infarct development. However, measurement of small cortical infarction would carry the risk of partial volume effects with CSF space.

Imaging our patients with a mean delay of 6 hours could raise the question whether early spontaneous recanalisation caused the inverse mismatch pattern. While in principle the (cross-sectional) finding of an inverse mismatch could be explained by complete or partial reperfusion, we believe that – considering the entire sequence of our findings – reperfusion is an unlikely sole explanation: Specifically, it does not explain the concentric lesion growth beyond the margins of the initial perfusion deficit in patients with initial inverse mismatch, match or mismatch.

If early reperfusion does not explain our findings, this implies that in the negative mismatch zone, cerebral areas have become severely damaged (as indicated by the ADC decrease and later infarction) without an underlying perfusion drop (normal MTT). At first sight this might seem surprising as it is has been shown in territorial ischaemia that ADC drops occur at a brain perfusion level below 34 ml/100g/min in rats [33] and below 15-20 ml/100g/min in gerbils [34]. On the other hand, ischaemia is obviously not the only "path" to cell damage. It may be sufficient that ischaemia and cell damage have occurred in the immediate vicinity. It is well known that neuronal damage leads to a release of cytotoxic substances such as potassium, glutamate, etc. and may induce spreading of depression-like events. Thus, a reasonable explanation for the inverse mismatch may be that the central ischaemia-induced lesion leads to perilesional cellular damage due to the release of cytotoxic agents. Perfusion may still be intact in the affected areas.

Indeed we believe that this is the most likely explanation for our results. Beside pathophysiological differences, potential therapeutic consequences can also be derived:

In territorial ischaemic infarction, ischaemia induces severe metabolic damage in a portion of the affected vascular territory (core zone), while in the remaining territory, collaterals sustain

perfusion for some time above a threshold level. In these areas at risk (penumbra), the most dominant pathophysiological factor is the impaired perfusion, and thus, presumably the most important therapy is rapid reperfusion (e.g. fibrinolysis).

In small subcortical stroke there is also a region in which severe metabolic damage occurs, however, because of the lack of collaterals there is no penumbra region. Therefore, cerebral areas adjacent to the core zone have normal perfusion. Damage to these "areas at risk" develops though a neurotoxic mechanism. It could be followed that in these patients, neuroprotective treatment approaches would be the first choice. Because clinical trials in ischaemic stroke are typically overwhelmingly recruiting territorial infarctions, it may well be that these were just the wrong patients. It may well be that those patients with small subcortical stroke, however, are the ones who benefit most from neuroprotective therapy.

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Legends:

Table 1 Individual lesion volumes on DWI (days 1, 2, 5) and T2-weighted images (day 5) with perfusion deficits (days 1, 2).

Figure 1 Inverse mismatch in two different patients (A-E and F-J): At day one (A&B, F&G) both have perfusion deficits on MTT maps that are significantly smaller than DWI lesions. At day two DWI lesion size increased and MTT deficit became smaller (C&D, H&I). Final lesion volume (E,J) is significantly larger than baseline DWI lesion and MTT deficit.

Table 1

Pat Nr	DWI day 1	DWI day 2	DWI day 5	MTT day 1	MTT day 2	T2 final
1 0M	0.50	1.90	1.96	0.59	0.00	1.55
2 0M	0.40	1.72	1.69	0.32	0.12	1.53
3 0M	0.44	1.00	1.98	0.48	0.55	2.63
4 IM	1.03	1.98	1.87	0.34	0.87	1.26
5 IM	3.06	3.43	3.05	0.85	0.60	3.10
6 IM	3.06	2.42	3.69	0.00	0.00	4.80
7 IM	2.13	4.09	5.54	1.06	1.50	6.00
8 IM	2.62	3.28	5.84	1.42	2.55	4.16
9 IM	1.79	2.82	2.46	0.59	1.19	3.20
10 IM	0.96	0.51	2.02	0.00	0.12	1.35
11 IM	4.82	5.34	4.18	1.95	1.66	3.52
12 IM	2.13	2.00	3.27	0.84	0.73	2.88
13 IM	1.12	2.81	2.45	0.13	0.37	3.47
14 IM	2.77	4.16	1.57	0.00	1.35	2.62
15 IM	3.19	3.17	4.32	0.00	0.00	4.98
16 IM	2.45	4.21	6.19	1.79	1.17	4.80
17 IM	0.65	1.89	3.92	0.48	0.25	2.59
18 MM	0.00	0.89	0.71	0.56	0.09	0.64
19 MM	1.52	5.19	4.10	2.25	1.13	6.02
mean	1.82	2.78	3.20	0.72	0.75	3.22
SD	1.26	1.39	1.56	0.69	0.70	1.59